(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date 27 January 2005 (27.01.2005)

PCT

(10) International Publication Number WO 2005/007193 A2

(51) International Patent Classification7: A61K 45/06

(21) International Application Number:

PCT/US2004/021641

(22) International Filing Date: 7 July 2004 (07.07.2004)

(25) Filing Language:

English

(26) Publication Language:

English

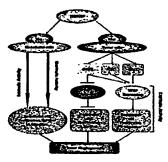
(30) Priority Data: 60/484,676

7 July 2003 (07.07.2003) US

(71) Applicant: VANDE WOUDE, George, F. [US/US]; 9451

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM). European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,



(71) Applicant and
(72) Inventor: ZHANG, Yu-Wen [CN/US]; 532 Briar Lane, N.E., Grand Rapids, MI 49503 (US).

(74) Agent: LIVNAT, Shmuel; Venable LLP, P.O. Box 34385, Washington, DC 20043-9998 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

(84) Title: INHIBITION OF TUMOR ANGIOGENESIS BY COMBINATION OF THROMBOSPONDIN-1 AND INHIBITORS OF VASCULAR ENDOTHELIAL GROWTH FACTOR

(54) Title: INHIBITION of Tumor Angiogenesis of this ligand-receptor pair is often associated with poor prognosis. The molecular basis for the malignant activity imparted by signaling of HGF/SF-Met in cancer cells has been attributed to its mitogenic and invasive properties. However, HGF/SF-Met indicated tumoringenesis. HGF/SF-Met in cancer cells has been attributed to its mitogenic and invasive properties. However, HGF/SF-Met in cancer cells has been attributed to its mitogenic and invasive properties. However, HGF/SF-Met in cancer cells has been attributed to its mitogenic and invasive properties. However, HGF/SF-Met in cancer cells has been attributed to its mitogenic and invasive properties. However, HGF/SF-Met in cancer cells has been attributed to its mitogenic and invasive properties. However, HGF/SF-Met in cancer cells has been attributed to its mitogenic and invasive properties. However, HGF/SF-Met in cancer cells has been attributed to its mitogenic and invasive properties. However, HGF/SF-Met in cancer cells in a dedition to inducine VBGE attributed to its mitogenic and invasive regulator of angiences in the very same tumor cells, in addition to inducine VBGE at the very same tumor cells, in addition to inducine VBGE in the very same tumor cells, in addition to inducing VEGF expression, HGF/SF dramatically down regulates TSP-1 expression. TSP shut off plays an important, extrinsic role in HGF/SF-mediated tumor development, as ectopic expression of TSP-1 markedly inhibited tumor formation through the suppression of angiogenesis. While VEGF induced expression is sensitive to inhibitors of several pathways, including MAP kinase, P13 kinase and Stat3, TSP-1 shut off by HGF/SF is prevented solely by inhibiting MAP kinase activation. Thus HGF/SF is a "switch" for turning on angiogenesis. TSP-1 is a useful antagonist to tumor angiogenesis, and therefore TSP-1 and agonist peptides and mimics, as well as inducers of TSP-1, have therapeutic value when used in conjunction with inhibitors of VEGP.